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CLINICAL REVIEW

Non-pharmacological interventions for improving sleep quality in patients on dialysis: systematic review and meta-analysis

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SUMMARY

We conducted a meta-analysis to summarise and quantify the effects of non-pharmacological interventions on sleep quality improvement in uraemic patients on dialysis. We defined the primary outcome as the change of sleep quality before and after interventions (evaluated by polysomonography or subjective questionnaires such as Pittsburgh sleep quality index, PSQI). The change of fatigue scales, inflammatory cytokines and adverse events were analysed as secondary outcomes. Twelve eligible randomised controlled trials and one prospective cohort study were identified. All three identified non-pharmacological interventions could result in a greater PSQI score reduction compared to controls: 1) cognitive-behavioural therapy (CBT) versus sleep hygiene education (standardised mean difference (SMD) 0.85, 95% CI 0.37–1.34); 2) physical training versus no training (SMD 3.36, 95% CI 2.16–4.57) and 3) Acupressure (including other acupoints massages) versus control (SMD 1.77, 95% CI 0.80–2.73). In terms of subscores, we found that CBT may shorten sleep latency, alleviate sleep disturbance and reduce the use of sleep medications. The finding of the cohort study suggested that intradialytic aerobic exercise training improved sleep quality in haemodialysis patients with restless leg syndrome. In conclusion, in dialysis-dependent patients, CBT could shorten sleep latency, alleviate sleep disturbance and reduce the use of sleep medications. Acupressure (including other acupoints massages) and exercise training are promising interventions but the results in these subgroups should be interpreted cautiously due to the concern of methodological quality and potential confounding factors.

Introduction

Chronic kidney disease (CKD) is characterised by a reduced glomerular filtration rate, increased urinary albumin excretion, or both [1,2]. Globally, 8%–16% of general population are living with CKD. The number of CKD patients who progress to the end stage renal disease (ESRD) and need dialysis is expected to grow annually [3], which made CKD one of the leading health problems and socioeconomic concerns in developed and developing countries [4].

Sleep disorders, despite various definitions, are common in the dialysis-dependent CKD population [5–8]. The reasons of the high prevalence of sleep problems in patients on dialysis are not fully enucleated, and previous studies reported some potential intrinsic and environmental causes, e.g., large body mass index, inflammatory status [9], low nutritional indices, presence of depression [10], inadequate dialysis [11–13] and overnight rostral fluid shift (fluid displaced from the lower limbs into the neck overnight) [14,15]. The sleep disorders contributed to poor quality of life in dialysis-dependent patients, which further deteriorate the health status of dialysis patients [16].

Apart from the contributory effect on poor quality of life [16,17], sleep problems are suggested to promote the development of risk factors for CKD progression (hypertension, type 2 diabetes and obesity). Furthermore, sleep disturbances might have a direct effect on the deterioration of kidney function in patients on dialysis [18]. Therefore, proper management of sleep disorders in patients on dialysis may yield favourable outcomes. There is currently no specified pharmaceutical treatment guideline for dialysis

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Abbreviations

CBT	cognitive-behavioural therapy
CIs	confidence intervals
CKD	chronic kidney disease
CRP	C-reactive protein
ESRD	end stage renal disease
ESS	Epworth sleepiness scale
HD	haemodialysis
HDL	high density lipoprotein
NNT/H	numbers needed to treat/harm
PD	peritoneal dialysis
PSG	polysomonography
PSQI	Pittsburgh Sleep Quality Index
QoL	quality of life
RCTs	randomised controlled trials
RLS	restless leg syndrome
RR	risk ratio
SMD	standardised mean difference
VAS	visual analogue scale

population, and benzodiazepines, non benzodiazepine, anxiolytics and melatonin are all prescribed for these patients. As data on drug therapy effects in dialysis patients are limited, the existing recommendations are mainly based on expert opinions [19]. As a result, practitioners should be cautious when prescribe drugs for sleep disorders in dialysis patients. Take insomnia for example, the pharmacological approach remains the most widely used intervention [20,21], meanwhile, concerns about drug tolerance, habituation, complications and excessive accumulation (especially for renal insufficiency patients) are frequently raised [22]. Kidney transplantation is the most effective way to correct uremic abnormality and may have positive impacts on sleep quality of CKD patients. Previous studies showed a significant improvement in sleep apnea hypopnoea syndrome, restless legs syndrome and chronic insomnia after renal transplantation [23–26]. However, there are also emerging researches failed to find the improvement of general sleep quality after kidney transplantation [27,28]. When interpreting the results of these conflicting studies, we should be aware that fluid overload (mainly contributed to obstructive sleep apnea) remission and immune suppressive therapy after kidney transplantation are the main confounding factors. Besides, study designs on this topic could not be randomised, which weakened the validity of these studies. Recently, growing evidence indicates favourable effects and less adverse events of non-pharmacological interventions (such as cognitive-behavioural therapy (CBT), acupuncture, exercise, bright light therapy, etc.) on primary insomnia [29], which are potential effective methods to improve the sleep quality in dialysis-dependent population as well. But the results of available clinical researches in dialysis-dependent population were inconsistent and were not summarised. The present systematic review and meta-analysis aims at comprehensively summarising and quantifying the effects of non-pharmacological interventions for improving sleep quality in dialysis-dependent patients, which will be helpful for evidence-based clinical decision-making.

Methods

The protocol of this review has been registered in PROSPERO (CRD42014006949) (www.crd.york.ac.uk/PROSPERO).

Search strategy and study selection

We conducted a comprehensive search of the medical literature using PubMed (inception to June 2014), EMBASE (inception to June 2014), Cochrane controlled trials register (issue 5, 2014), Web of Science (inception to June 2014) and http://clinicaltrials.gov/(date of search: June 24th 2014). The PubMed search terms (both as medical subject headings and free text terms) were: (renal dialysis or renal replacement therapy or kidney disease) and (disorders of initiating and maintaining sleep or parasomnias or dyssomnias or intrinsic sleep disorder or insomnia or sleep apnea syndrome or nightmares or interrupted sleep or sleep disorders). Detailed PubMed search strategy was submitted as web extra material, and the search terms were adapted for the other electronic data sources. We additionally searched the reference lists of the original reports, reviews, letters to the editor, case reports, guidelines and meta-analyses retrieved through the electronic searches. There was no restriction on language of publications.

We selected the studies in two steps. Firstly, two review authors (Bo Yang and Jiaruo Xu) independently screened the titles and the abstracts. Secondly, the full text of potentially eligible studies was retrieved and assessed independently by the same two review authors. The pre-specified eligibility criteria are as follows: 1) randomised controlled trials (RCTs) or prospective cohort studies; 2) dialysis-dependent patients with end stage renal disease; 3) pharmacological interventions comparable in experimental groups and in control groups; 4) sleep quality evaluated before and after interventions; 5) the factors to be studied were non-pharmacological interventions; 6) placebo control (e.g., sham acupressure) or standard control (standard non-pharmacological interventions e.g., sleep hygiene education). Studies using other unrelated interventions were eligible, as long as these were administered to both the experimental and control groups. We excluded studies with the following properties: 1) patients with renal cell carcinoma; 2) patients with unstable or acute clinical situations; 3) presence of psychiatric disorders. If duplicate publication was identified, we used the one with the most relevant information. We abandoned all the retracted research. Any disagreement between review authors was resolved by consensus, adjudicated with the support of a third review author (Qiang Xue).

Data extraction

All data were extracted independently by two review authors (Tingting Wei and Jing Xu) into a predesigned data collection form (Microsoft Office Excel 2007; Microsoft Corp, Redmond, Washington, USA). All data extraction was then checked by a third review author (Chaoyang Ye). The following data were extracted for each study: study design; number of centres; geographical location of the study; patient characteristics (age; proportion of female patients; disease status; dialysis status and baseline sleep quality); sample size; duration of interventions; detailed relevant interventions; concomitant interventions allowed; and total number along with the detailed information about adverse events reported. We defined our primary outcome as the change of sleep quality before and after study (evaluated by polysomonography (PSG) or subjective questionnaires such as Pittsburgh sleep quality index (PSQI) [30] and its constituent components). As another common syndrome in patients on dialysis, change of fatigue scales was combined as secondary outcome; inflammatory cytokines and adverse events were also analysed as secondary outcomes. Domains used to evaluate the risk of bias for each study were also documented: methods used to generate the randomisation schedule; allocation concealment and blinding. We attempted to contact the original investigators in order to obtain further

information if necessary. Data were extracted as intention-to-treat analyses (available case analysis), wherever trial reporting allowed this.

Assessment of risk of bias

Assessment of risk of bias was performed independently by two review authors (Bo Yang and Changlin Mei), with disagreements resolved by discussion. Risk of bias ratings for each randomised controlled trial was evaluated according to the quality domains in the Cochrane risk of bias tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and any other potential threats to validity. Risk of bias for each domain was rated as high (seriously weakens confidence in the results), unclear or low (unlikely to seriously alter the results). For cohort studies, we did not formally assess their methodological quality, nor did we pool their results into meta-analysis. Instead, we only carried out a systematic review on them.

Data synthesis and statistical analysis

For RCTs, heterogeneity among studies was evaluated by calculating the I^2 statistic and Chi-square test (assessing the P value). If the P value was less than 0.10 and I^2 exceeded 50%, we consider heterogeneity substantial. Random effects model was used to combine the data if significant heterogeneity existed. Dichotomous data were summarised as risk ratio (RR) and numbers needed to treat/harm (NNT/H). Continuous data were pooled as standardised mean difference (SMD), along with 95% confidence intervals (CIs), respectively. For ordinal outcomes derived from measurement scales, when the number of categories is large, they were analysed in meta-analyses as continuous data. Whilst ordinal scales with less categories were made into dichotomous data by combining adjacent categories together, as recommended by Cochrane handbook for systematic reviews of interventions [31]. To avoid the bias induced by the inappropriate choice of the cut-point when we convert the ordinal outcomes into dichotomous data, we defined scales with categories $\geq$4 are large. When studies with multiple intervention groups were included, we combined groups and created a single pair-wise comparison to avoid double-counts of the participants in the 'shared' intervention group [31]. We conducted pre-specified subgroup analyses according to the type of interventions and baseline dialysis status of the subjects. Sensitivity analyses were carried out by excluding outliers and small sample size studies to test the stability of our results. We only performed a systematic descriptive review on the cohort studies.

Review Manager (RevMan) [Computer program] Version 5.2. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used to generate forest plots as well as funnel plots. The funnel plots were assessed for evidence of asymmetry, and possible publication bias or other small study effects. We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines in reporting our findings [32].

Results

The search strategy initially identified 5756 records, 117 of which were potentially relevant to our systematic review and the full texts of them were retrieved for further evaluation (Fig. 1). Of these, 104 were excluded according to the inclusion/exclusion criteria, leaving a total of 13 eligible articles ultimately: twelve RCTs [33–44] involving 709 patients for quantitative synthesis and one prospective cohort study [45] for systematic review only.

Study characteristics

Characteristics of the included studies are shown in Table 1.

Subjects in the twelve RCTs were all dialysis-dependent. Two trials [41,43] studied patients on peritoneal dialysis (PD) while others on haemodialysis. Four hundred and forty-five patients in seven trials [34,35,37,40–42,44] had chronic sleep disorders at baseline. Among these seven trials, the definitions of sleep disorders at the time of enrolment were clearly described and identical (PSQI scores of at least five points) in four [34,37,41,42]. But in the other three RCTs [35,40,44], the definition was unclear. Four types of non-pharmacological interventions were studied in these twelve trials: physical exercises (including intradialytic training) [33,44]; acupressure and other acupoints massages [34–37,40]; cognitive-behavioural therapy [38,41,42] and the change of dialysis modality [39,43]. Placebo control (sham acupuncture) was performed in three trials [34–36] in the acupuncture subgroup. These three trials contain multiple and shared eligible intervention groups, we processed them as recommended in the Cochrane handbook [31]. Other trials used standard control, which was described as sleep hygiene education or usual care in the original article. Nine trials [34–38,40–42,44] used the same rating scale (PSQI) to assess sleep quality, while Yurtkuran et al. [33] used a visual analogue scale (VAS) method, which is not a validated scale; Bro et al. [43] reported the sleep quality as a component of modified quality of life

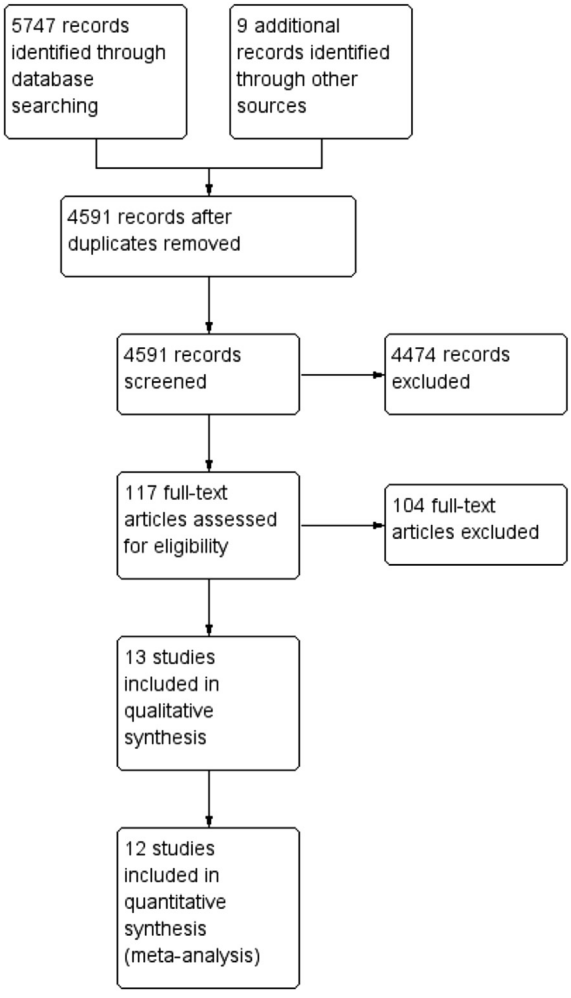

Fig. 1. Flow diagram of studies included.

Table 1
Characteristics of included studies.

Study	Study design	Geographical location	Study population	Mean age y	Sample size (male)	Interventions/ Exposures in each arm	Outcomes	Duration of intervention	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Bro et al. 1999 [43]	RCT	Denmark	Adequately dialyzed patients with high or high-average peritoneal transport characteristics	54.2; 50.2	13(8); 12(8)	1) APD; 2) CAPD	SF-36; blood haemoglobin; plasma creatinine; urea; glucose; potassium; sodium; ionized calcium; phosphate; albumin; standard bicarbonate; dialysate creatinine; urea; glucose; plasma intact parathyroid hormone; estimates of dialysis adequacy; QoL	6 mo	Sealed envelopes containing the treatment allocation were arranged in groups of ten and used for the randomisation procedure	Unclear	Open-labelled	Open-labelled	Drop-outs were described and reasons for drop-outs were unlikely to be related to true outcome	The results of all outcomes described in methods were reported
Tsay et al. 2003 [35]	RCT	Taiwan	Adult HD patients complaining of sleep disturbance	Overall 55.52	35(17); 35(10); 35(15)	1) Acupressure to the following acupoints: HT7 in ears and hand, and K11, by finger pressure of 3–4 kg. The time of interventions consisted of 5 min of massage to relax the person and 9 min of acupoints massage (3 min per acupoints). Treatment was given three times per week for 4 wk; 2) Sham acupressure to locations with no acupoints; 3) Usual care alone	PSQI	4 wk	Unclear	Unclear	The patients and care takers were blind to treatment allocation	The assessors were blind to treatment allocation	Drop-outs were excluded but the distribution of drop-outs among the treatment groups was not clearly described	The results of all outcomes described in methods were reported
Tsay et al. 2004 [34]	RCT	Taiwan	Adult HD patient with PSQI scores of five points or over and BDI scores of 10 points or higher	Overall 58.16	36; 36; 36 gender: 36 M overall	1) Acupressure to the following acupoints: K-1 in both feet, St-36, GB-34 and Sp-6 in both legs, The treatment was limited to 15 min. Treatment was given 3 times per week; 2) Transcutaneous Electrical Acupoint	PSQI; PFS; BDI	4 wk	Unclear	Unclear	Unclear	Unclear	Drop-outs were described and reasons for drop-outs were unlikely to be related to true outcome	The results of PSQI score was collected but not provided. We failed to get further information from the author

(*continued on next page*)

Table 1 (*continued*)

Study	Study design	Geographical location	Study population	Mean age y	Sample size (male)	Interventions/ Exposures in each arm	Outcomes	Duration of intervention	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
						Stimulation (TEAS) was given to the same acupoints as in intervention group 1. Each treatment took 15 min. Treatments were given three times per week; 3) Routine unit care only								
Tsay et al. 2004a [36]	RCT	Taiwan	Adult HD patient, and complaint of fatigue	57.23; 60.49; 56.81	35; 35; 36 gender: 36 M overall	1) Acupressure to the following acupoints: K-1 in both feet, St-36, GB-34 and Sp-6 in both legs, the treatment was limited to 15 min. Treatment was given three times per week; 2) Sham acupressure to locations with no acupoints; 3) Usual care alone	PSQI; PFS; fatigue (VAS); BDI	4 wk	Unclear	Unclear	Unclear	Unclear	No drop-out description	The results of PSQI score was collected but not provided. We failed to get further information from the author
Yurtkuran et al. 2007 [33]	RCT	Turkey	HD patients	38; 41	20(11); 20(13)	1) Yoga class twice a week and usual care; 2) Usual care only	Pain intensity (VAS); fatigue (VAS); sleep disturbance (VAS); grip strength; plasma urea; plasma creatinine; plasma calcium; plasma alkaline phosphatase; plasma phosphorus; plasma cholesterol; plasma HDL-cholesterol; plasma triglyceride; haematocrit (%); erythrocyte	3 mo	Computer-generated table of random numbers	Unclear	Open-labelled	Physician who did the examination was blind	Drop-outs were described and reasons for drop-outs were unlikely to be related to true outcome	The results of all outcomes described in methods were reported
Chen et al. 2008 [41]	RCT	Taiwan	Adult patients undergoing maintenance PD who had severe sleep disorder[a]	51.9; 48.7	13(7); 13(7)	1) Sleep hygiene education and four 1-h-weekly treatment sessions of CBT; 2) Sleep hygiene education	PSQI; FSS; haemoglobin; serum albumin; calcium; phosphorus; blood urea nitrogen; serum creatinine; IL-6; IL-1β; IL-18; TNFα	4 wk	Computer-generated randomised numbers	The sequence was concealed until the interventions were assigned	Open-labelled	Open-labelled	No drop-outs after randomisation	The results of all outcomes described in methods were reported

Parker et al. 2008 [39]	RCT	USA	Adult HD patients	46.1 overall	4; 3 gender 3 M overall	1) HD was administered in warm condition (dialysate bath temperature 37 °C); 2) HD was administered in cool condition (dialysate bath temperature 35 °C)	Skin temperature; PSG	The same as the HD duration	Unclear	Unclear	Open-labelled	Sleep stages were manually scored by blinded investigator	No drop-outs after randomisation	The results of all outcomes described in methods were reported
Sakkas et al. 2008 [45]	Prospective cohort study	Greece	Adult patients on maintenance HD who were diagnosed RLS	48; 70	7(5); 7(5)	1) The exercise training regime always consisted of 45 min continuous cycling using a bedside cycle ergometer at 45−50 rpm between the second and third hour of a 4-h HD session. The exercise resistance was set between 65% and 75% of their maximum power capacity assessed at the beginning of the training and reassessed and adjusted every 2 wk by a submaximal cycling test. Each training session included 5 min warm-up and 5 min cool down periods. 2) No training	IRLS severity score; SF-36; sleep diary score; ESS score; Zung depression scale score; SGA; muscle function; haematocrit; haemoglobin; ferritin; transferring; Kt/V	16 wk	–	–	–	–	–	–
Afshar et al. 2011 [44]	RCT	Iran	Adult patients on conventional maintenance HD with sleep disturbances	21.6; 19.4	14(14); 14(14)	1) Regular aerobic training which consisted of 5 min of warm-up and 10−30 min of stationary cycling during the 1st two hours of each dialysis session; 2) No training	PSQI; serum CRP; serum leptin	8 wk	Unclear	Unclear	Unclear	Unclear	No drop-outs description	The results of all outcomes described in methods were reporter
Chen et al. 2011 [42]	RCT	Taiwan	Adult patients undergoing maintenance HD who had chronic sleep disorders[a]	57; 59	37(17); 35(13)	1) 30-min tri-weekly treatment sessions of CBT and sleep hygiene education; 2) Sleep hygiene education	PSQI; hs-CRP; IL-1β; IL-18; ox-LDL; FSS; BDI; BAI	6 wk	Computer-generated random numbers	Sequence was concealed until the interventions were assigned	Open-labelled	Open-labelled	Drop-outs were described and reasons for drop-outs were unlikely to be related to true outcome	Some of the components of the PSQI scale were not provided and we got no response when contact with the author

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Table 1 (*continued*)

Study	Study design	Geographical location	Study population	Mean age y	Sample size (male)	Interventions/ Exposures in each arm	Outcomes	Duration of intervention	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Nasiri et al. 2011 [40]	RCT	Iran	Adult HD patient. PSQI scores of five points or over.	48.68; 47.81	31(19); 31(18)	1) One hour after starting dialysis, the patient rests on back and takes deep inspiration by nose and expiration by mouth for five times. After ear shenmen, hand shenmen and neiguan and yungchung were pressed. three times/week; 2) Usual care	PSQI; sleep log	4 wk	Unclear	Unclear	Unclear	Unclear	No drop-outs description	The results of all outcomes described in methods were reported
Shariati et al. 2012 [37]	RCT	Iran	Adult ESRD patients routinely receiving afternoon maintenance HD. PSQI scores of five points or over.	53.5; 55.5	22(12); 22(11)	1) Intradialytic acupoints massage (He7, Li4 and sp6) three times/week; 2) Routine care.	PSQI	4 wk	Simple randomisation method	Unclear	The care providers did not know what type of treatment patients received	The interviewer did not know what type of treatment patients received	Drop-outs were described and reasons for drop-outs were unlikely to be related to true outcome	The results of all outcomes described in methods were reported
Rambod et al. 2013 [38]	RCT	Iran	Adult patients on HD	49.07; 50.72	43(29); 43(24)	1) Listen to the Benson's relaxation technique CD twice a day and perform it simultaneously at home after training session; 2) Routine treatment and care	PSQI	8 wk	Table of random numbers	The nurses and physicians were blind to the allocation of the subjects	The nurses and physicians were blind to the outcome measures. The interventionist who taught the Benson's relaxation technique was blind to the aim of the study	The researcher assistant who collected the data was blind to the study groups and the intervention. The statistician who performed the data analysis was kept blinded to the allocation.	Drop-outs were described and reasons for drop-outs were unlikely to be related to true outcome	The results of all outcomes described in methods were reported

Abbreviations: APD automated peritoneal dialysis; BAI Beck anxiety inventory; BDI Beck depression inventory; CAPD continuous ambulatory peritoneal dialysis; CBT cognitive-behavioural therapy; CRP: C-reactive protein; ESRD end stage renal disease; ESS Epworth sleepiness scale; FSS Fatigue severity scale; HD haemodialysis; HDL: high density lipoprotein; IRLS international RLS study group rating scale; PD peritoneal dialysis; PFS Piper fatigue scale; PSG polysomonography; PSQI Pittsburgh sleep quality index; QoL: quality of life; RCT randomised controlled trial; RLS restless legs syndrome; SGA subjective global assessment scale; VAS visual analogue scale.

[a] Sleep disturbances were defined as: 1) difficulties initiating and maintaining sleep or 2) early morning awakenings with inability to return to sleep, which satisfied the criteria for insomnia in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

(QoL) scale while Parker et al. [39] used PSG to assess the sleep quality objectively. Fatigue and depression were measured in five RCTs [33,34,36,41,42], with self-administered questionnaires. Durations of intervention were various according to the types of interventions. Studies on physical exercises (including intradialytic training) usually lasted for 8–16 wk; acupressure and other acupoints massages usually for 4 wk; cognitive-behavioural therapy for 4–8 wk and studies on change of dialysis modality took months.

We included only one prospective cohort study involving fourteen patients [45]. We found that in a great number of publications claiming to be 'cohort studies', the design features, however, were usually retrospective or cross-sectional. According to the existing 'evidence hierarchies', these kind of study design were more likely to be open to bias; we considered it was not helpful to include them into this systematic review. In the only included cohort study, Sakkas [45] studied intradialytic aerobic exercise training for the haemodialysis (HD) patients with restless leg syndrome. The researcher in this study reported quality of sleep with sleep diary score.

Risk of bias

Risk of bias ratings for each trial (Table 1) were assessed with the Cochrane risk of bias tool and 'Risk of bias summary' figure details all of the judgements (Fig. 2). All the RCTs described as 'randomised', and there were six among them reporting the detailed randomisation methods. However, only three trials described allocation concealment in detail, so we could not assess the sufficiency of this domain in the rest trials. Due to the nature of non-pharmacological interventions, performing blinding methods were usually impossible. Even 'sham acupuncture' could only blind the allocated intervention to the patients but not the caregivers. So we rated all the RCTs at high risk of bias in this domain. This may induce performance bias in the studies. Blinding of outcome assessment was sufficiently carried out in five trials. Drop-outs and the reasons were clearly reported in eight trials, and overall less than 15% subjects dropped out, which may not induce significant attrition bias. Three studies [36,41,42] reporting primary outcomes as global PSQI score, but the results of its constituent components were unavailable. We tried to contact the authors to get further information but failed. We also found that the methodological quality varied between subgroups regardless of the year trials were conducted. All three RCTs [38,41,42] in CBT subgroup showed a good quality and low risk of bias. However four out of five trials focusing on acupressure and other acupoints massages [34–36,40] were not well conducted and reported.

Evidence from randomised trials

Global PSQI score

Seven RCTs involving 423 patients were pooled. As showed in Fig. 3, there was a significant global PSQI score reduction in the intervention groups over the control (SMD 1.50, 95% CI 0.91 to 2.09; $I^2 = 85\%$). Excluding studies with small sample size (<30) did not change the effect size (SMD 1.44, 95% CI 0.86–2.01) nor the degree of heterogeneity ($I^2 = 83\%$, $P < 0.001$). Subgroup analyses showed that compared with control groups, all of the three types of non-pharmacological interventions could result in a greater PSQI score reduction after study: 1) cognitive-behavioural therapy versus sleep hygiene education (SMD 0.85, 95% CI 0.37 to 1.34; $I^2 = 56\%$, $P = 0.10$); 2) physical training versus no training (SMD 3.36, 95% CI 2.16–4.57) and 3) acupressure and other acupoints massages versus control (SMD 1.77, 95% CI 0.80 to 2.73; $I^2 = 87\%$, $P < 0.001$). There were also two studies focusing on dialysis modality. But the results of this subgroup were not combined with other RCTs', due to the obvious clinical heterogeneity. Bro et al. [43] found that the sleep quality (assessed with self-administered questionnaire) were not different between continuous ambulatory peritoneal dialysis and automated peritoneal dialysis. But long time has passed since the trial was completed. Given the improvement in peritoneal dialysis techniques in these years, the conclusions in this research may be out of date. Therefore, we should interpret its finding with caution. Parker et al. performed an orphan study [39] on the cool dialysate (35 degree centigrade) and concluded that cool dialysate during HD may improve nocturnal sleep the night following treatment.

Constituent components of PSQI questionnaire

Non-pharmacological interventions showed different effects on each component of sleep quality. According to our results, CBT may

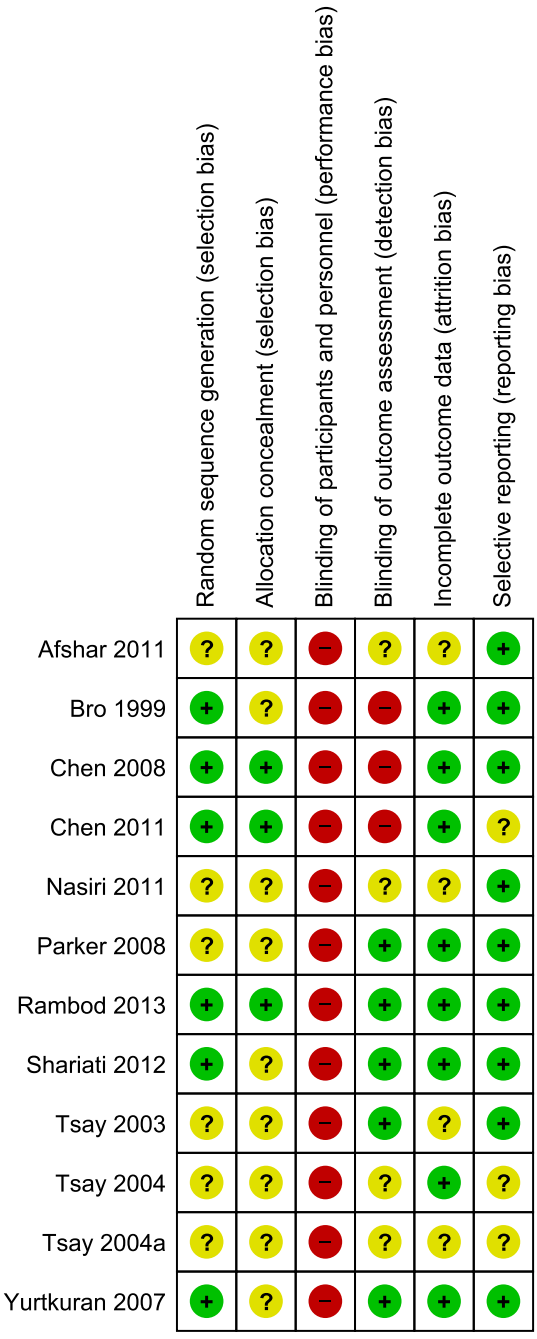

Fig. 2. Risk of bias.

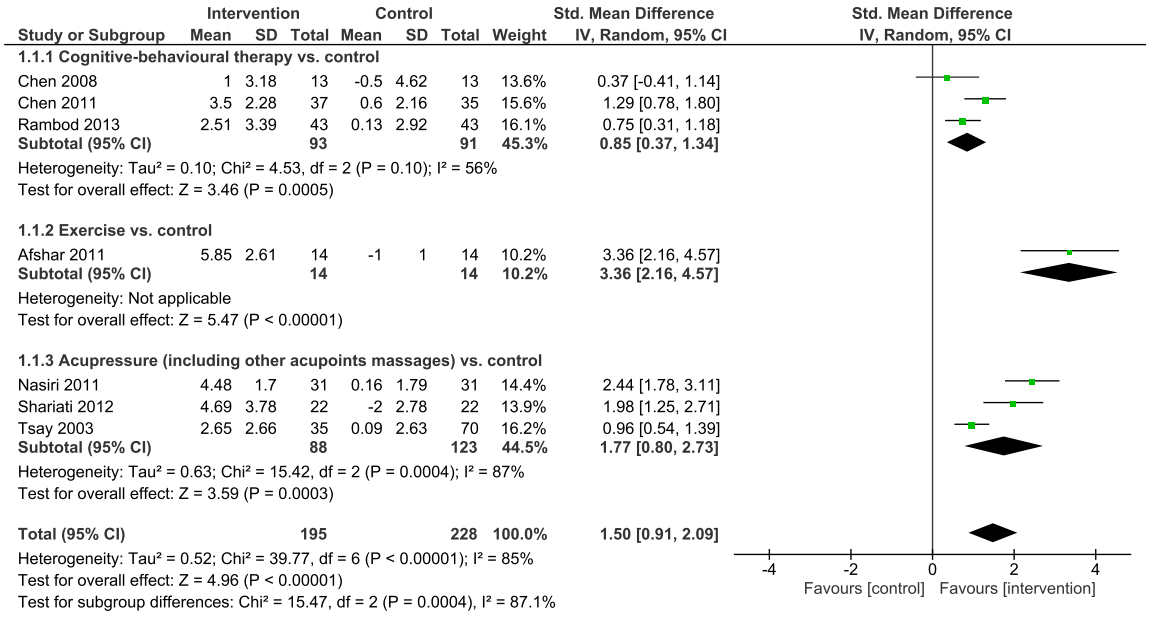

Fig. 3. Reduction of global Pittsburgh sleep quality index among patients receiving non-pharmacological interventions versus control. SD, standard deviation; IV, inverse variance; 95% CI, 95% confidence interval.

shorten sleep latency (SMD 1.33, 95% CI 0.46–2.19), alleviate sleep disturbance (SMD 0.95, 95% CI 0.56 to 1.35; $I^2 = 0\%$, $P = 0.84$) and reduce the use of sleep medications (SMD 0.73, 95% CI 0.29–1.17). But in other domains of PSQI, the results did not support the positive effect of CBT over control: subjective sleep quality (SMD 0.44, 95% CI −0.28 to 1.17; $I^2 = 64\%$, $P = 0.10$), sleep duration (SMD −0.50, 95% CI −1.29 to 0.28), habitual sleep efficiency (SMD −0.43, 95% CI −1.68 to 0.83; $I^2 = 86\%$, $P = 0.007$) and daytime function of patients (SMD 0.28, 95% CI −0.10 to 0.65; $I^2 = 0\%$, $P = 0.42$) (Figs. 4–10).

Five trials studied acupressure and other acupoints massages, all the investigators chose to perform the intervention intradialytically. Since the patients need not to spend extra time on the intervention, this may improve the compliance of the patients. Acupressure and other acupoints massages may ameliorate subjective sleep quality (SMD 0.85, 95% CI 0.34 to 1.37; $I^2 = 77\%$, $P = 0.004$), shorten sleep latency (SMD 0.88, 95% CI 0.59 to 1.17; $I^2 = 0\%$, $P = 0.38$), lengthen sleep duration (SMD 1.27, 95% CI 0.63 to 1.92; $I^2 = 75\%$, $P = 0.02$), increase habitual sleep efficiency (SMD 1.09, 95% CI 0.79 to 1.39; $I^2 = 0\%$, $P = 0.48$) and improve daytime function of patients (SMD 0.73, 95% CI 0.08 to 1.38; $I^2 = 79\%$, $P = 0.009$). We did not find its benefit in alleviating sleep disturbance (SMD 1.86, 95% CI −0.40 to 4.12; $I^2 = 97\%$, $P < 0.001$) and reducing the use of sleep medications (SMD 0.25, 95% CI −0.09 to 0.59; $I^2 = 31\%$, $P = 0.24$) (Figs. 4–10).

Change of fatigue scales

Combination of five RCTs yield that non-pharmacological intervention can significantly alleviate fatigue (SMD 0.66, 95% CI 0.44 to 0.88; $I^2 = 0\%$, $P = 0.58$) (Fig. 11). Subgroup analysis showed that this result was stable in the intervention of CBT (SMD 0.77, 95% CI 0.36 to 1.18; $I^2 = 0\%$, $P = 0.51$) and acupressure (including other acupoints massages) (SMD 0.70, 95% CI 0.40 to 0.99; $I^2 = 0\%$,

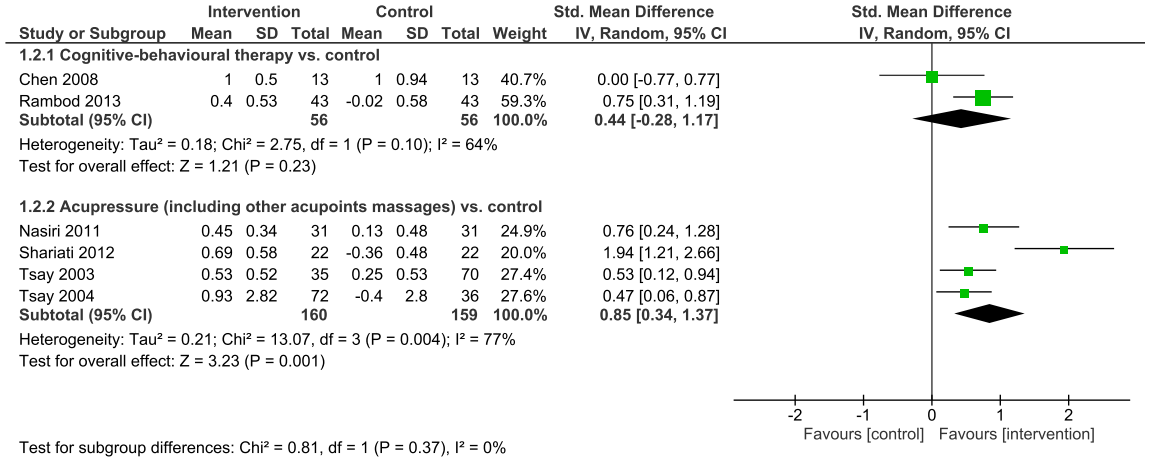

Fig. 4. Change of subjective sleep quality in Pittsburgh Sleep Quality Index among patients receiving non-pharmacological interventions versus control. SD, standard deviation; IV, inverse variance; 95% confidence interval.

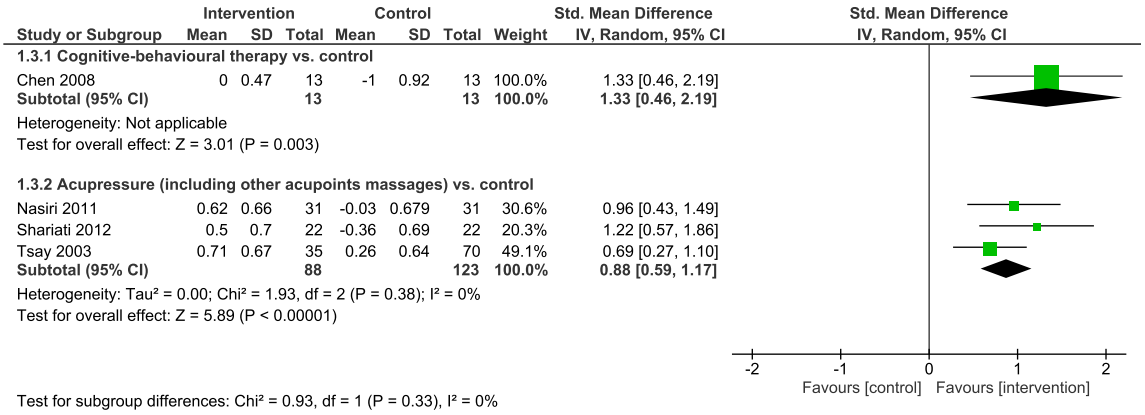

Fig. 5. Change of sleep latency in Pittsburgh Sleep Quality Index among patients receiving non-pharmacological interventions versus control. SD, standard deviation; IV, inverse variance; 95% CI, 95% confidence interval.

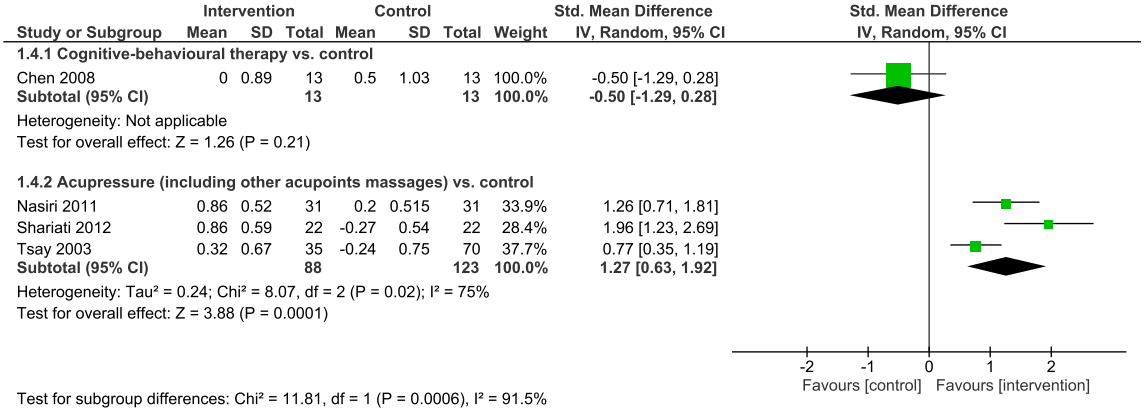

Fig. 6. Change of sleep duration in Pittsburgh Sleep Quality Index among patients receiving non-pharmacological interventions versus control. SD, standard deviation; IV, inverse variance; 95% CI, 95% confidence interval.

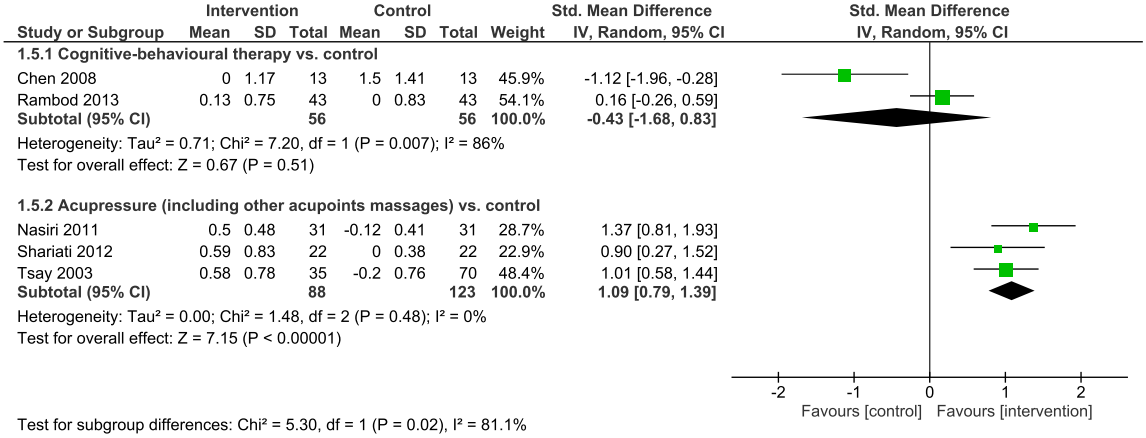

Fig. 7. Change of habitual sleep efficiency in Pittsburgh Sleep Quality Index among patients receiving non-pharmacological interventions versus control. SD, standard deviation; IV, inverse variance; 95% CI, 95% confidence interval.

$P = 0.57$), but physical exercise could not alleviate subjective feeling of fatigue (SMD 0.24, 95% CI −0.38–0.86).

There are not enough data to combine inflammatory cytokines changes. Two trials conducted by Chen et al. [41,42] assessed the level of inflammatory markers, but the researchers expressed their outcomes in percentages rather than absolute measures. We could only find that CBT can potentially reduce serum high-sensitive C-reactive protein, interleukin-18 and oxidised low-density lipoprotein from their original research. No information on adverse events was available.

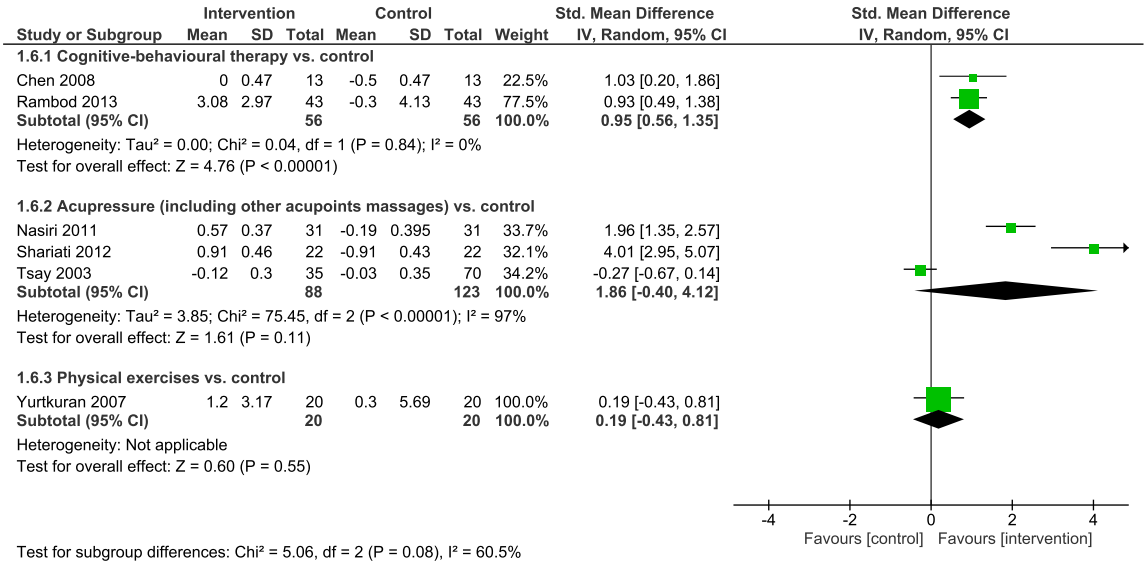

Fig. 8. Change of sleep disturbance in Pittsburgh Sleep Quality Index among patients receiving non-pharmacological interventions versus control. SD, standard deviation; IV, inverse variance; 95% confidence interval.

Evidence from cohort studies

Only one non-random study met our criteria [45]. The finding of this study suggested a favourable sleep quality improvement (assessed with sleep diary score) of intradialytic aerobic exercise training on HD patients with restless leg syndrome (RLS) (SMD 1.52, 95% CI 0.28–2.76). Besides, daytime function (assessed with Epworth sleepiness scale (ESS) scale) was better in training group (SMD 1.79, 95% CI 0.48–3.01).

Discussion

Principal findings and possible interpretations

This meta-analysis and systematic review provides evidence for improving sleep quality with non-pharmacological interventions in dialysis-dependent patients. Eleven out of 13 studies included subjects on HD, and two studies focused on PD patients. This homogeneity of patients reduced the clinical heterogeneity but may not provide a good model for the whole spectrum of dialysis-dependent population. Involved non-pharmacological interventions covered several most commonly used ones. Except for the domain of blinding methodological qualities of the studies in CBT and exercise subgroups were relatively high, but trials focusing on acupressure (including other acupoints massages) were of low quality.

CBT comprises several therapeutic strategies including sleep education, sleep hygiene, stimulus control, sleep restriction, relaxation training, and cognitive therapy, which target a broad range of symptoms and etiologic factors [46]. According to the combined results, we found that CBT could shorten sleep latency, alleviate sleep disturbance and reduce the use of sleep medications. This group of results indicates that the proven effects of CBT [21,47–49] in primary sleep disorders might be generalised to the dialysis-dependent ESRD population. In the CBT subgroup, we also found that daytime function and subjective sleep quality had a trend of improvement in combined results, but this improvement did not reach statistical significance. This was interesting and we explored the possible explanations. In the original PSQI questionnaire, we found that two subjective questions ('During the last month, how would you rate your sleep quality overall?' and 'During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done') affecting these components are likely to be influenced by confounding factors (e.g., depression, fatigue and anxiety) which are very common in dialysis-dependent patients [50,51]. Thus, the true effect of interventions was unlikely to be revealed. The sample size in this subgroup was small. In addition, the 'CBT' in the trial conducted by Rambod et al. [38] was only a part rather than a complete CBT intervention protocol, which may induce clinical heterogeneity. Limited number of studies prevented us from performing sensitivity analyses in this subgroup to test the robustness of the original results. Apart from the sleep quality, Chen et al. [41,42] reported the reduction of inflammatory markers by CBT as secondary outcomes. The interrelationship between sleep quality and inflammatory markers was complex. Former research on non-renal disease subjects suggested that elevated inflammatory markers are frequently associated with sleep disorders (mainly abnormal sleep duration) [52–54]. A study in HD patients also revealed that prevention and treatment of inflammation were essential to prevent morbidity and mortality due to sleep disorders [9]. But after examining the study design of this publication, we decided that the conclusions above were not directly supported by the results. In other words, authors go beyond the evidence in their conclusions. According to the current evidence, elevated inflammatory markers may either be a manifestation of sleep disorders or be a causation of sleep disorders. Whether CBT improves sleep quality through suppressing the inflammatory protein is still unknown.

Acupressure (including other acupoints massages) revealed a potent effect in global PSQI score reduction and most of its components. But methodology quality in this subgroup is our major concern (Fig. 2). Two comprehensive systematic reviews have tried to evaluate acupuncture for treating insomnia in non-renal disease population [55,56]. However, both of them failed to draw any safe conclusions owing to the methodological limitations of available literature. We could only regard acupressure (including other acupoints massages) as potentially effective interventions. Intradialytic acupressure is not as time-consuming as other non-pharmacological therapies, and no additional training for patients is needed, making it a possible option for non-pharmacological interventions [57].

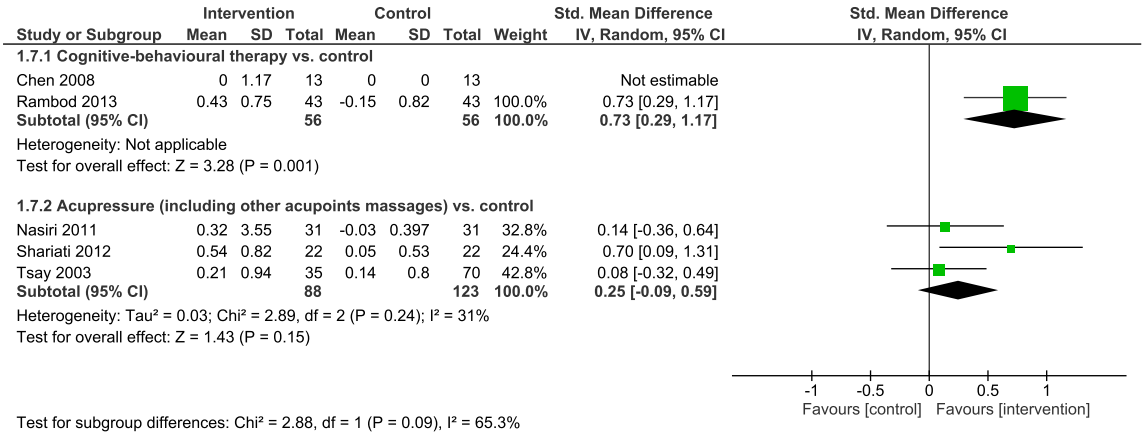

Fig. 9. Change of sleep medication using in Pittsburgh Sleep Quality Index among patients receiving non-pharmacological interventions versus control. SD, standard deviation; IV, inverse variance; 95% confidence interval.

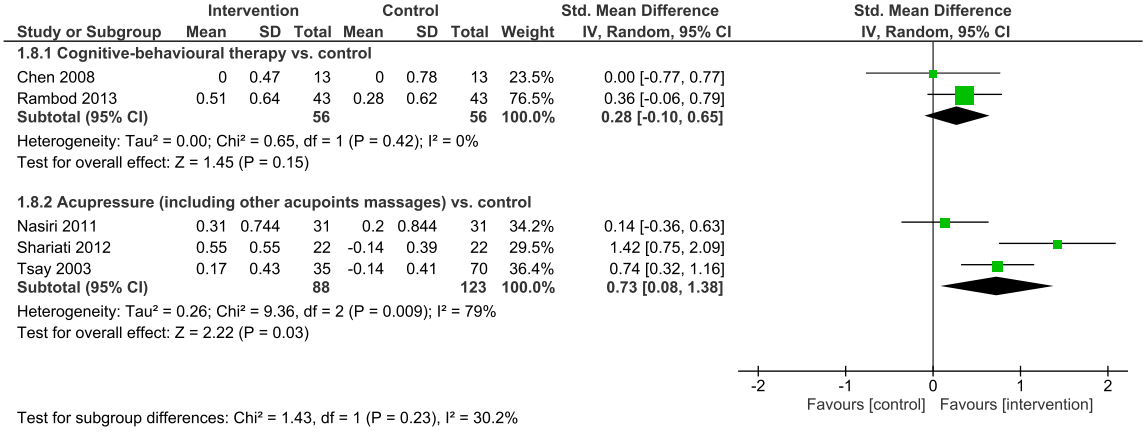

Fig. 10. Change of daytime function in Pittsburgh Sleep Quality Index among patients receiving non-pharmacological interventions versus control. SD, standard deviation; IV, inverse variance; 95% CI, 95% confidence interval.

The combined results revealed that non-pharmacological intervention could significantly alleviate fatigue. Patients' subjective feeling of fatigue is strongly influenced by the presence of anaemia, which is common in kidney disease patients. However, three [34,36,42] of the five trials reporting the fatigue scale scores did not control this confounding factor by measuring haemoglobin before and after interventions, nor did they provide treatment protocols for anaemia. Yurtkuran et al. [33] tested erythrocyte and haematocrit and found they significantly increased after intervention. Adequacy of dialysis is another confounding factor affecting patients' subjective feeling of fatigue, but only two studies [33,41] monitored the Kt/V or serum creatinine before and after interventions. Due to the flaws in the original researches, we could not tell the improvement of fatigue resulted from non-pharmacological intervention, the improvement of anaemia or the increase of uraemic toxins clearance. Therefore, we should interpret the results with caution.

Cardiopulmonary fitness, physical function and removal of urea or phosphate were also reported to be improved by aerobic exercise during HD session [58–60], and these beneficial effects may contribute to the improvement of sleep quality. We retrieved only one RCT and one prospective cohort study on this topic, and refrained from making definite conclusion because of the limited data available.

Strengths and limitations

There are several strengths of this review. Firstly, the review question is an important issue correlated closely to doctors' daily practice, and our extensive search of the relevant literature provided a comprehensive assessment of the review question. Secondly, all the included trials evaluated sleep quality with validated PSQI questionnaire. This homogeneity is the basis of reliability of data combination. Besides, we studied the PSQI assessment questionnaire by ourselves and understood the objective, the target population and we analysed the questionnaire in depth and tried to find potential confounding factors in relation to our review question. Some potential limitations should be discussed. As we know, the 'gold standard' for sleep quality assessment is PSG. However, for economic consideration, subjective questionnaire instead of PSG was applied in most researches, which may produce potential bias. Furthermore, none of the studies reported adverse events, although CONSORT statement [61] required adverse events data be reported. Without the information of adverse effects, we could not assess the safety of the studied non-pharmacological interventions. Finally, blinding of participants and personals was not performed in any of the trials. This lead to a relatively low methodological quality (assessed with Cochrane risk of bias tool).

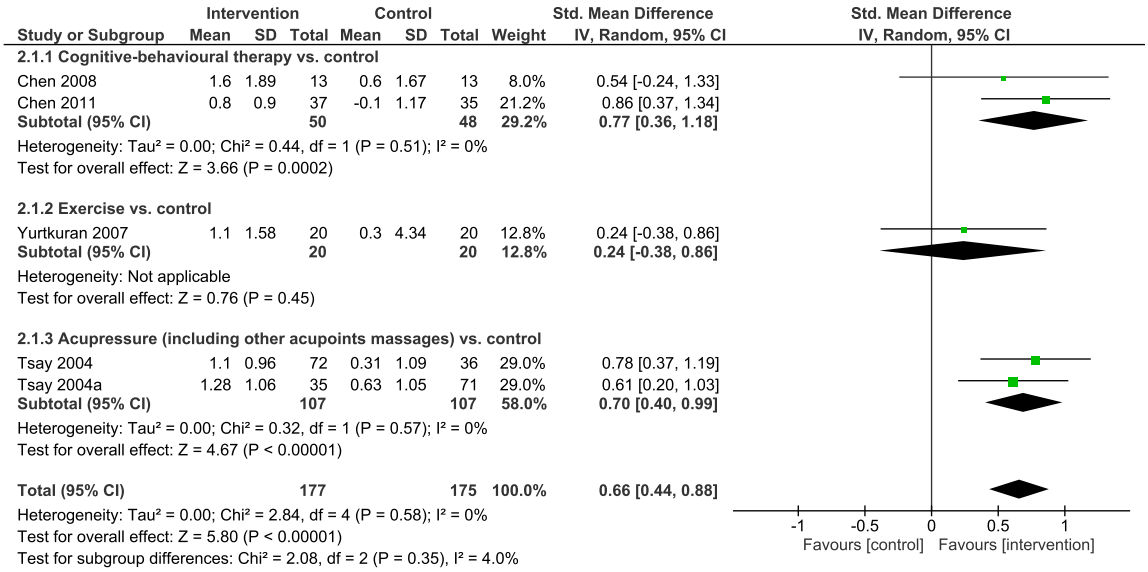

Fig. 11. Change of subjective fatigue questionnaire results among patients receiving non-pharmacological interventions versus control. SD, standard deviation; IV, inverse variance; 95% CI, 95% confidence interval.

Comparison with other studies

To date, there is no systematic review or meta-analysis assessing the efficiency and safety of non-pharmacological interventions on sleep quality improvement in patients on dialysis. Several published meta-analyses on primary sleep disorder population revealed favourable effect of non-pharmacological therapy [55,56,62,63]. We tried to find out whether these conclusions could be generalized to the dialysis-dependent population. Our results revealed that non-pharmacological interventions in patients on dialysis showed similar effects to non-CKD population on sleep disorders.

Conclusions and implications for future research

In the dialysis-dependent ESRD patients, CBT, physical training and acupressure (including other acupoints massages) could result in improvement of sleep quality by showing a greater PSQI score reduction. CBT could shorten sleep latency, alleviate sleep disturbance and reduce the use of sleep medications. Acupressure (including other acupoints massages) and exercise training are promising interventions but the results in these subgroups should be interpreted cautiously due to the concern of methodological quality and potential confounding factors. Further study focusing on acupuncture (including its variants) should be undertaken with better control of confounding and other bias. Exercises could be divided into three types for strength, flexibility or endurance improvement. It is interesting to explore how these three types improve the sleep quality in dialysis-dependent patients, and whether exercises increase the incidence of adverse events such as acute heart failure. Since the sleep problems are common in patients at all stages of CKD, the impact of non-pharmacological interventions on sleep quality of pre-dialysis CKD patients remains to be further investigated.

Contributors

Zhiguo Mao acts as guarantor for the validity of the study report. Study concept and design: Zhiguo Mao and Changlin Mei. Acquisition of data: Bo Yang and Jiaoruo Xu. Extraction of data: Tingting Wei and Jing Xu. Checking of data: Qaing Xue and Chaoyang Ye. Analysis and interpretation of data: Bo Yang and Jiaruo Xu. Drafting of the manuscript: Bo Yang and Tingting Wei. Critical revision of the manuscript for important intellectual content: Zhiguo Mao and Changlin Mei.

Practice points

1 Growing evidence indicates favourable effects and less adverse events of non-pharmacological interventions on primary sleep disorders.
2 Cognitive-behavioural therapy can improve the general sleep quality in dialysis-dependent chronic kidney disease patients.
3 Acupressure (including other acupoints massages) and exercise training are promising interventions for improving sleep quality in patients on dialysis.

Research agenda

1 The safety of non-pharmacological interventions for sleep quality improvement in dialysis-dependent patients should be explored in future studies.
2 The impact of non-pharmacological interventions on sleep quality of pre-dialysis CKD patients remains to be further investigated.
3 More good quality evidence is needed to further prove the validity and safety of acupressure (including other acupoints massages) and exercise training.
4 Exercises could be divided into three types for strength, flexibility or endurance improvement. It is interesting to study how these three types improve the sleep quality in dialysis-dependent patients, and whether exercises increase the incidence of adverse events.

Conflict of interest

None declared.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2014.11.005.

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